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Long-term Topical Nitrogen Mustard Treatment Does Not Induce Pulmonary Fibrosis in MF Patients

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Eleven patients with mycosis fungoides had X-ray examinations of their lungs before, during and after topical treatment with mechlorethamine. The mean number of treatments was 163, ranging from 28 to 300 treatments within a period of 1 to 13 years (mean 7.8 years). Each exposure to the skin of mechlorethamine was between 20 and 40 mg giving a cumulative dosage in the range from 1.120 mg to a maximum of 12.000 mg. We looked for potential lung damage from mechlorethamine vapours, such as fibrosis of the lungs, but found none. Thus, we conclude that topical treatment with mechlorethamine of patients with mycosis fungoides is not only an effective treatment, but also a safe therapy.

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Mycosis fungoides belongs to the malignant cutaneous T cell lymphomas. The disease is progressive and exhibits a fatal course in some patients. Topical treatment with nitrogen mustard has been used in the treatment of mycosis fungoides since 1959, and several studies have shown increased survival rates related to this therapy (1–12). The toxicity of nitrogen-mechlormetamine (mechlorethamine) is primarily extrapolated from the known analogue sulphur mustard (S-mustard) used in chemical warfare (2). The long-term hazards of exposure to S-mustard are known to give chronic bronchitis and cancer of the respiratory tract.

The aim of this study was to examine the risk of chronic lung damage among patients in long-term treatment with mechlorethamine.

PATIENTS AND METHODS

Since 1972 all patients in our department with histologically verified early mycosis fungoides have been treated with topical mechlorethamine. Initially, all patients are treated with daily whole-body topical application for 2 weeks. The maintenance treatment is given as two applications every second week to every second month, depending on the clinical response to therapy. From 1972–78 we used Erasol®, which is mechlorethamine in an alcohol solution, and from 1979 we used the chemical equivalent Mustine®, which is a powder dissolved in sterile water. The method of application is by brushing with a gauze brush or a compress of moistened linen. Following a demand by Occupational Health Authorities, safety precautions have been installed since 1983. Mechlorethamine applications are given in a separately ventilated room, where the patient is kept for 30 min after the treatment. The nurse administering the treatment wears protective devices: a gas mask, rubber apron, thick rubber gloves and boots (3).

Under almost similar environmental and treatment conditions, Van Vloten et al. (13) have found that the nurse and the patient are exposed to a concentration of mechlorethamine of 0.036 mg/m^3.

Mechlorethamine is a clear and odourless liquid with a boiling point of 75°C. It has an evaporation pressure of 1/60 ppm, corresponding to the evaporation of 0.01–0.1 mg mechlorethamine from a 30-cm^2 bowl containing 10 mg mechlorethamine at 25°C. The compound is highly instable and is hydrolysed in water. The ability of penetration is high, especially through the skin and to a lesser degree through rubber (3).

We selected 11 patients with mycosis fungoides (7 males and 4 females, mean age 67.5 years, range 52–81 years), who had received a long-term treatment with topical mechlorethamine and where we had X-rays both before the therapy started, during and after therapy. All X-rays were examined and compared by the same observer (NK), who was not aware of the number of therapies given to each patient. Pulmonary function tests were not performed.

RESULTS

Three out of 11 patients had normal X-ray of the chest before and after treatment. Five out of 11 had unchanged and insignificant pleural infiltrations before and after the treatment. Two out of 11 had unchanged small fibrotic infiltrations before and after treatment. One patient died of hemothorax not related the treatment with mechlorethamine. At autopsy, this patient had areas of the lung with tumour masses of lymphoma, but no fibrosis was found. The mean duration of treatment was 81.2 months (14–150 months), and the mean number of treatments was 163 treatments (28–300). The mean time of observation was 7.8 years with a range of 1–13 years. No case of increased lung fibrosis was found.

DISCUSSION

Our knowledge of the effect on man of exposure to S-mustard is primarily related to workers from factories producing S-mustard, and the use of this agent in chemical warfare during World War I, in Ethiopia in 1936, and in the Iran/Iraq war in the 1980's. S-mustard is extremely toxic, inducing CNS symptoms such as headache, dizziness, nausea and vomiting, extensive skin damage with erythema, blisters, and toxic epidermal necrolysis within 12–24 h, ocular symptoms in 4–5 h and pulmonary oedema within 24 h. Seven out of 11 Danish fishermen had acute symptoms following accidental exposure to S-mustard gas from getting leaking mustard gas shells into their nets. They required hospital treatment for about 1 month. One of these, a 30-year-old previously healthy non-smoker, developed a severe obstructive airway disease (4). The-long term effects of nitrogen mustard have been studied among war pensioners suffering from S-mustard gas poisoning in 1917–18, and among factory workers manufacturing both S-mustard and mechlorethamine in the period 1929–45 from Japan and Germany. The findings have been increased mortality rates for cancer of the respiratory tract,

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ranging between 1.3–33 times above expected rates in different studies (3,6). Chronic airway disease, mostly categorized as chronic bronchitis, was also found, with an increased mortality rate between 3–10 times (5, 6).

Much of the information on the toxicity of mechlorethamine arises from conclusions of analogy from S-mustard. This is probably also basically valid. However, the level of exposure is substantially different from extreme peak exposures in the warfare situation to long-term intermittent low-dose exposure in the dermatological scenario.

The side effect of the dermatological use of topical mechlorethamine is an increased risk of developing squamous cell carcinoma or basal cell carcinoma of the skin (12), contact dermatitis or contact urticaria. Some patients also complain of a headache following treatment, but this may in part be psychological. Topical mechlorethamine does not influence the bone marrow function or induce signs of immune suppression (7). The mutagen potency has also been examined in the same group of patients that participated in the present study. No significant differences in levels of sister chromatid exchange in lymphocytes were found (8).

Some pharmacological agents used in the treatment of cancer have been linked to pulmonary toxic side effects. Pulmonary fibrosis and more acute cases of pneumonitis have been reported after MOPP (mechlorethamine, oncovine, prednisolone, procabazine) chemotherapy for Hodgkin's disease (10,11). However, the way of exposure is different. In cancer chemotherapy the drugs are delivered intravenously, in dermatology exposure takes place through the skin and through vapours during the treatment.

In conclusion, mechlorethamine is an efficacious topical chemotherapy of MF (1, 12). Long-term skin application does not seem to induce an increased risk of lung damage. This is in accordance with the concentrations of nitrogen mustard in the air as measured by Van Vloten et al. (13). The extent of measures to protect the medical personnel applying the treatment should be decided by occupational health authorities and may differ from one country to another (3, 13).

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